Does regular blood transfusion prevent progression of cerebrovascular lesions in children with sickle cell disease?

Valentine Brousse, Lucie Hertz-Pannier, Yann Consigny, Jean-Louis Bresson, Robert Girot, Elsa Mirre, Gérard Lenoir, Mariane Montalembert

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ORIGINAL ARTICLE

Does regular blood transfusion prevent progression of cerebrovascular lesions in children with sickle cell disease?

Valentine Brousse · Lucie Hertz-Pannier · Yann Consigny · Jean-Louis Bresson · Robert Girot · Elsa Mirre · Gérard Lenoir · Mariane de Montalembert

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Abstract A retrospective study was conducted to assess changes in cerebrovascular lesions, as assessed by magnetic resonance (MR) imaging and angiography in 18 children with sickle cell disease (SCD) receiving optimised chronic transfusions for primary stroke prevention (abnormal transcranial Doppler flow, nine patients, median follow-up 14.3 months (range, 7.9–48.9)) or secondary stroke prevention (nine patients, median follow-up 59.6 months (range, 11.0–127.9)). An experienced neuroradiologist blinded to patient data reviewed the 41 MR scans (median/patient, three (2–4)). Standard scores were used to evaluate parenchymal and vascular abnormalities at baseline and last follow-up. Within-patient score changes evaluated using Wilcoxon's paired rank test indicated lesion progression in the secondary-prevention group (p=0.027). Optimised transfusion therapy does not prevent progression of cerebral vasculopathy in SCD children with a history of stroke.

Keywords Sickle cell disease · Stroke · Transfusion · Brain imaging

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V. Brousse · M. de Montalembert
Reference Centre for Haemoglobinopathies,
Hôpital Necker, APHP,
Paris, France

V. Brousse (✉) · E. Mirre · G. Lenoir · M. de Montalembert
Paediatrics Department, Hôpital Necker Enfants Malades,
149 rue de Sèvres,
75015 Paris, France
e-mail: valentine.brousse@nck.aphp.fr

L. Hertz-Pannier
Department of Paediatric Radiology, Hôpital Necker, APHP,
Paris, France

L. Hertz-Pannier
INSERM U663, Paris Descartes University,
Paris, France

Y. Consigny
Department of Hepatology, Hôpital Beaujon, APHP,
Paris, France

J.-L. Bresson
Clinical Research Unit, Hôpital Necker, APHP,
Paris, France

R. Girot
Haematology Laboratory, Hôpital Tenon, APHP,
Paris, France

Cerebral vasculopathy is not only among the most severe complications of sickle cell disease (SCD) in children, but also extremely common, with an overall prevalence by magnetic resonance imaging (MRI) of up to 55% [1]. Clinical evidence of stroke occurs by 20 years of age in 11% of patients with SCD [2] and the incidence of stroke is 1.02% per year between 2 and 5 years of age. In addition to stroke, cerebral vasculopathy can cause cognitive impairments that adversely affect educational outcomes [3–5].

Transfusion therapy has been found effective for primary and secondary stroke prevention in patients with SCD. In the randomised STOP study of children whose transcranial Doppler (TCD) results indicated a high risk of stroke [6], regular blood transfusions reduced the risk of stroke by 90%. Similarly, transfusion therapy was effective in reducing the risk of recurrent stroke, although transient neurological events were not decreased [7, 8]. Stopping a regular transfusion regimen has been associated with a high rate of stroke recurrence [9]. In children whose TCD results

returned to normal after regular transfusions for at least 30 months, stopping the transfusions was associated with recurrence of abnormal blood-flow velocities and with stroke [10]. Despite the convincing evidence that transfusion is beneficial in children at high risk for neurological complications, no data are available on long-term magnetic resonance imaging or angiography (MRA) in children with SCD who receive regular transfusions. Longitudinal studies involving serial TCD studies suggest that transfusion therapy may markedly reduce both blood-flow velocity in the middle cerebral arteries and red-cell sickling [11]. However, conventional angiography studies have shown mild progression of vascular lesions over time, despite an initial decrease in vessel irregularity [12], suggesting that transfusions may fail to stabilise or improve the vascular lesions.

Our objective was to assess changes in MRI and MRA evidence of cerebrovascular disease over time in children with SCD receiving optimised chronic transfusion therapy.

Materials and methods

Patients

We reviewed the records of all consecutive children with homozygous SCD who received chronic transfusion therapy for primary or secondary stroke prevention at the Necker Enfants Malades Hospital, Paris, France, from June 1994 to June 2006. We identified 18 patients, nine boys and nine girls. Among them, nine were started on primary prevention after TCD screening showed abnormal blood-flow velocities (time-averaged mean of the maximum velocity≥200 cm per second) and nine were put on secondary prevention after sustaining a first stroke. These last patients had experienced a cerebrovascular accident before the implementation of annual TCD screening as standard care and have subsequently the longest follow-up. Chronic transfusion therapy was initiated within 1 month after the stroke or abnormal TCD screen. Patients received either transfusions or exchange transfusions according to the haemoglobin level at admission. We recorded the following data: age at the first stroke or abnormal TCD screen, time of transfusion therapy initiation and results of monthly complete blood cell counts and haemoglobin S (HbS) determinations.

Brain imaging

MRI and MRA were performed at 1- to 2-year intervals in all patients. Because these investigations were part of standard care and the study design was retrospective, informed consent from the patients and families was not required.

Before 1998, there was no standard protocol, but MR evaluation included at least T1- and T2-weighted sequences and 3D time-of-flight MRA images. After 1998, MR evaluation routinely included 5-mm-thick T1- and T2-weighted images and 4-mm-thick FLAIR images, as well as 3D time-of-flight 1.2-mm-thick MRA images. All images were reviewed twice by an experienced neuroradiologist (LH-P), who was unaware of patient identity, history and date of imaging. Image quality was scored from 1 to 3 (1, unacceptable movement artefact or missing sequence; 2, minor movement artefact and 3, high-quality images). We excluded the six investigations that received a score of 1. Scoring systems adapted from Steen [1] were used to evaluate parenchymal abnormalities (lacunae, leucoencephalopathy, cerebral atrophy and encephalomalacia) and vascular abnormalities (arterial tortuosity, stenosis, occlusion and moya-moya); scores could range from 0 to 16 (Table 1).

Statistical analysis

Quantitative variables were expressed as median (range). MRI scores, MRA scores and total MR scores at baseline and at last follow-up were compared in each patient using Wilcoxon paired rank tests.

Results

Median age at first stroke (n=9) was 7.6 years (3.0–10.8) and median age at first abnormal TCD was 6.5 years (4.0–12.8). Median follow-up was 59.6 months (11.0–127.9) in the stroke group and 14.3 months (7.9–48.9) in the abnormal-TCD group. Mean pre-transfusion HbS percentage was 30.8±4.7 in the stroke group and 33.3±9.8 in the abnormal-TCD group. Corresponding mean post-transfusion HbS percentages were 21.4±2.9 and 22.9±6.5, respectively.

The 18 patients had 41 MR evaluations included in the analysis (Table 2). The median number of MR evaluations per patient was 3 (2–4). In the stroke group, the median total score (MRI+MRA) was 10 [2–22] at baseline and 12 [3–26] at last follow-up (p=0.027). Thus, progression of the MR abnormalities occurred despite adequate transfusion therapy in patients with a history of a single stroke episode. In the abnormal-TCD group, the median total score was 0 (0–7) at baseline and 0 (0–10) at last follow-up.

Discussion

Cerebrovascular lesions as assessed by MR worsened in children with SCD who had a history of stroke, despite chronic transfusion therapy that kept the HbS percentage

Table 1 Method for scoring abnormalities found by magnetic resonance imaging and angiography, adapted from Steen et al. [1]

Lacunae	**Leuco-encephalopathy**	**Atrophy**	**Encephalomalacia**
0: absence	0: absence	0: absence	0: absence
1: <1 cm unilateral	1: ≤3 cm unilateral	1: ≤1 unilateral territory	1: ≤1 unilateral territory
2: >1 cm unilateral	2: >3 cm unilateral	2 >1 unilateral territory	2 >1 unilateral territory
3: <1 cm bilateral	3: ≤3 cm bilateral	3 ≤1 bilateral territory	3 ≤1 bilateral territory
Tortuosity	**Stenosis/occlusion of right and left MCA, ACA, ICA**		**Moya moya**
0: absence	0: absence		0: absence
1: unilateral	1: <50%		1: unilateral
2: bilateral	2: ≥50%		2: bilateral
	3: 100%		

MCA middle cerebral artery, *ACA* anterior cerebral artery, *ICA* internal carotid artery

within the range usually considered protective [7]. In the abnormal-TCD group, MR evaluation showed no change, but the follow-up was too short to draw conclusions from this finding. Although age was comparable in the two groups, the total MR score at baseline was lower in the abnormal-TCD group, in keeping with the hypothesis that increased cerebral blood-flow velocity antedates the development of MR abnormalities.

The worsening MR findings in the stroke subgroup were clinically silent in eight of the nine patients; the remaining patient experienced a second stroke episode. Stroke recurrence has been reported previously in children receiving monthly transfusions for SCD [7, 8] however, in these previous studies, HbS levels were greater than 30% in most of the patients and were most likely to be high among patients who experienced recurrent stroke or transient ischemic attacks. The rate of recurrent stroke was 1.9 per 100 patient-years in a retrospective study where most patients had less than 30% HbS [8]. It was only 1.15 per 100 patient-years in our study, suggesting that 30% may be a good HbS target level. However, despite the optimal transfusion regimen used in our study, cerebrovascular lesions worsened in the patients who had a history of stroke. Although the long-term consequences of this finding are unclear, children with progressive cerebrovascular disease may experience cognitive impairments and an increased risk of moya-moya disease.

The reasons for the inability of regular transfusions to halt the progression of cerebrovascular disease in children with SCD and a history of stroke deserve discussion. Factors that may be relevant include the genetic makeup and lesion severity at treatment onset. Conceivably, specific genetic influences may result in progressive vascular lesions that fail to respond to transfusion therapy. In keeping with this possibility, a small minority of children in the STOP study had persistent increases in cerebral blood-flow velocities despite transfusion therapy

Table 2 Clinical data and scores of patients

Patient	Date of birth	Inclusion criteria	Date transfusion program started	Date of first MR	Quality score	Initial score	Date of last MR	Quality score	Final score
1	15/02/00	Stroke	1/09/05	15/09/05	3	10	15/08/06	2	10
2	26/06/86	Stroke	1/01/1994	15/02/94	3	14	17/01/03	3	23
3	31/08/90	Stroke	1/07/96	15/06/98	3	13	6/06/06	3	12
4	23/06/88	Stroke	1/05/95	1/03/96	2	9	1/03/03	3	10
5	14/06/00	Stroke	1/11/03	1/01/05	3	4	11/07/06	3	5
6[a]	13/08/92	Stroke	1/02/96	1/08/96	2	9	6/04/06	3	23
7	16/01/91	Stroke	1/02/01	26/01/01	3	22	4/01/06	3	26
8	30/03/90	Stroke	1/10/98	1/01/99	3	19	30/05/06	3	25
9	18/09/97	Stroke	1/02/02	16/07/02	2	2	1/12/04	3	3
10	4/07/97	TCD	1/05/05	8/05/05	3	0	18/07/06	3	0
11	23/12/98	TCD	1/12/04	1/01/05	3	1	11/17/2006	3	1
12	23/09/93	TCD	1/01/04	1/02/04	3	6	28/06/06	3	8
13	19/08/01	TCD	1/06/05	1/09/05	3	0	1/05/06	3	0
14	16/11/99	TCD	1/08/05	15/08/05	3	7	11/08/06	3	10
15	5/02/99	TCD	1/01/05	1/08/05	3	0	7/08/06	3	0
16	6/05/97	TCD	1/06/05	24/06/05	3	0	3/08/06	3	0
17	11/11/97	TCD	1/11/02	1/08/02	2	0	30/08/06	2	0
18	20/09/91	TCD	1/04/04	19/07/04	2	0	12/07/06	3	1

[a] Patient 6 experienced recurrence of overt stroke despite chronic exchange transfusion program

[6]. Another possibility is that the vascular lesions may become refractory to treatment once they have crossed a severity threshold. The absence of disease progression in the abnormal-TCD group may be related to the short follow-up.

Our study has limitations inherent to the retrospective design. Advances in imaging techniques in recent years have increased the ability to detect lesions [1]. In our study, however, the same imaging protocol was used from 1998 to 2006, so that a role for technical changes in the worsening of MR findings is unlikely. In addition, the quality score filter strongly reduced the risk of spurious interpretation of low quality images. Both reproducibility and accuracy of imaging criteria are critical issues. We are unaware of other longitudinal studies using the Steen et al. scoring system. In this study, all scans were reviewed twice by an experienced (>15 years) pediatric neuroradiologist blinded to any clinical data. After complete analysis of randomly ordered scans of all mixed patients, the longitudinal sequence of each patient was reviewed allowing a retrospective determination of the accuracy of the previous readings. This internal check proved a high degree of reproducibility as only in two cases did discrepancies lead to a third determination. In the original Steen et al. study, the inter observer variability was deemed low and all discrepant cases could be solved by consensus. We used a validated score[1] for within-patient comparisons over time. However, the score items do not reflect a single pathophysiological process. For this reason, and because the number of patients was limited, a separate analysis of microvessel and macrovessel damage was not feasible. Such an analysis would help to identify the mechanisms that lead to cerebrovascular disease progression.

In conclusion, our findings do not challenge the usefulness of chronic transfusion in children with SCD and a history of stroke or abnormal TCD. They establish that, in patients with a history of stroke, SCD-related cerebrovascular damage continues to progress despite chronic transfusion keeping HbS levels below 30%. The long-term consequences of cerebrovascular disease progression are unclear. Little is known about changes in brain parenchyma damage after haematopoietic stem cell transplantation for severe SCD [13]. Therefore, we do not know whether early transplantation would be more effective in preserving a normal neurodevelopmental pattern than chronic transfusion in at-risk SCD children. Knowledge of the mechanisms involved in SCD-related brain damage would help to determine the best treatment strategy for preventing this devastating complication.

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